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Subject: Tumor/Genetic Markers

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DESCRIPTION:

Serum tumor markers are molecules or substances shed by a tumor into the circulation where they can be detected and quantitated. Noncirculating tumor markers include those that can be detected histochemically or cytogenetically on a tissue sample.

Since serum tumor markers can also be detected in normal or benign lesions, significantly elevated circulating levels may occur with malignancy by one or more of the following mechanisms: overexpression of the antigen by malignant cells; a large tumor burden; or slower clearance of the marker. For example, since the liver clears most tumor markers, liver abnormalities (whether benign, malignant, or inflammatory) may elevate tumor marker concentrations due to impaired clearance. Because most tumor markers are not unique to malignancy, cut-off points must be established for normal versus abnormal marker levels.

The clinical applicability of tumor markers depends on how their measurements are used to influence the management of the patient and whether these management changes will result in an improvement in net health outcome.

POSITION STATEMENT:

Biochemical Markers of Alzheimer Disease (AlzheimAlert™, ADmark®CSF, DISCERN™) **Note:** Genetic testing for Alzheimer disease (see MCG 05-82000-28) may be offered	Measurement of cerebrospinal fluid biomarkers, including but not limited to tau protein, amyloid beta peptides, or neural thread proteins, as an adjunct to clinical diagnosis in members with mild cognitive impairment or mild dementia due to Alzheimer disease is considered **experimental or investigational.** The evidence is insufficient to determine the effects of the technology on health outcomes.

along with analysis of cerebral spinal fluid levels of the tau protein and amyloid-b peptide 1-42. This group of tests may be collectively referred to as the Admark™ Profile, offered by Athena Diagnostics.	Measurement of urinary biomarkers of Alzheimer disease, including but not limited to neural thread proteins, is considered **experimental or investigational.** The evidence is insufficient to determine the effects of the technology on health outcomes.
Breast Tumor Markers	CA 15-3 (CA 27.29 or Truquant RIA) **meets the definition of medical necessity** for the following indications: • As an aid in the management of Stage II and Stage III breast cancer members. Serial testing for CA 15-3 assay values should be used in conjunction with other clinical methods for monitoring breast cancer • As an aid to predict recurrent breast cancer in members with previously treated Stage II or Stage III disease • As an aid in monitoring response to therapy in members with Stage IV breast cancer. A partial or complete response to treatment will be confirmed by declining levels. A persistent rise of CA 27-29 levels despite therapy strongly suggests progressive disease. CA 15-3 (CA 27.29 or Truquant RIA) is considered **experimental or investigational**, as there is insufficient clinical evidence to support the use of CA 15-3 (CA 27.29 or Truquant RIA) as a screening test for breast cancer. There is a lack of clinical data to permit conclusions on efficacy and net health outcomes.
Cancer Antigen 125 (CA-125)	CA-125 testing **meets the definition of medical necessity** in individuals with symptoms suggestive of ovarian cancer; symptoms may include: • Swelling of the abdomen (ascites) • Gastrointestinal symptoms (e.g., gas, bloating, long-term stomach pain, indigestion) • Bleeding between periods or after menopause • Pelvic pain • Feeling of pressure in the pelvis • Leg pain.

	CA-125 testing **meets the definition of medical necessity** in individuals with other gynecologic malignancies, such as endometrial cancer, in whom baseline levels of CA-125 have been shown to be elevated. CA-125 testing in asymptomatic individuals is considered **experimental or investigational.** There is insufficient clinical evidence to support the use of CA-125 testing as a screening technique for ovarian cancer.
Cardiovascular Disease Risk Panels (Cardiovascular risk panels may include: Applied Genetics Cardiac Panel; Boston Heart Advanced Risk Markers Panel; Cleveland HeartLab CVD Inflammatory Profile; Genetiks Genetic Diagnosis and Research Center Cardiovascular Risk Panel; Genova Diagnostics CV Health Plus Genomics™ Panel; Health Diagnostics Cardiac Risk Panel; Metametrix Cardiovascular Health Profile; MI-HEART Ceramides; Spectracell LPP™.)	Cardiovascular disease risk panels, consisting of multiple individual biomarkers intended to assess cardiac risk (other than simple lipid panels*****), are considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes. *****A simple lipid panel is generally composed of the following lipid measures:Total cholesterol; LDL cholesterol; HDL cholesterol; Triglycerides. Certain calculated ratios, such as the total/HDL cholesterol may also be reported as part of a simple lipid panel. Other types of lipid testing, i.e., apolipoproteins, lipid particle number or particle size, lipoprotein (a), etc., are not considered to be components of a simple lipid profile.
Gene Expression Profiling for Colorectal Cancer	Gene expression profiling (eg, ColonSentry®, BeScreened™-CRC) is considered **experimental or investigational** for colorectal cancer screening. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.
Tumor-Informed Circulating Tumor DNA	Tumor-informed circulating tumor DNA testing (e.g., Signatera™) is considered **experimental or investigational** for all indications. The evidence is insufficient to determine the effects of the technology on health outcomes.
Circulating Tumor DNA and Circulating Tumor Cells for	The use of circulating tumor DNA and/or circulating tumor cells is considered **experimental or investigational** for all other indications not included in this policy. The evidence

Cancer Management (Liquid Biopsy)	is insufficient to determine the effects of the technology on health outcomes. **Note:** This does not address the use of blood-based testing for driver mutations to select therapy in non-small-cell lung cancer or metastatic colorectal cancer, use of blood-based testing for use of liquid biopsy for detection or risk assessment of prostate cancer, the use of AR-V7 circulating tumor cells for metastatic prostate cancer, or liquid biopsy to select targeted treatment for breast, ovarian, or pancreatic cancer. A list of FDA-approved targeted treatments and companion diagnostic tests can be found at: fda.gov/medicaldevices/vitro-diagnostics/list-cleared-orapproved-companiondiagnostic-devices-vitro-and-imagingtools.
Cutaneous Melanoma (DecisionDx DiffDx- Melanoma)	Gene expression testing, including but not limited to the Pigmented Lesion Assay (PLA), in the evaluation of members with suspicious pigmented lesions is considered **experimental or investigational**. Gene expression testing, including but not limited to the myPath Melanoma test, in the evaluation of members with melanocytic lesions with indeterminate histopathologic features is considered **experimental or investigational**. Gene expression testing, including but not limited to DecisionDx-Melanoma, in the evaluation of members with cutaneous melanoma is considered **experimental or investigational** for all indications. The evidence is insufficient to determine the effects of the technology on health outcomes.
Microarray-Based Gene Expression Profile Testing for Multiple Myeloma Risk Stratification (MyPRS™/MyPRS Plus™)	Microarray-based gene expression profile testing for multiple myeloma is considered **experimental or investigational** for all indications. The evidence is insufficient to determine the effects of the technology on health outcomes.
Molecular Analysis, Including Liquid Biopsy (circulating tumor DNA/ctDNA), for Targeted Therapy or	**EGFR Testing** Analysis of somatic variants in exons 18 through 21 (such as G719X, L858R, T790M, S678I, L861Q) within the

Immunotherapy of Non-Small-Cell Lung Cancer (NSCLC)	epidermal growth factor receptor (EGFR) gene **meets the definition of medical necessity** to predict treatment response to an EGFR tyrosine kinase inhibitor (TKI) therapy (e.g. erlotinib [Tarceva®], gefitinib [Iressa®], afatinib [Gilotrif®], or nswerctin [Tagrisso]) in members with advanced lung adenocarcinoma, large cell carcinoma, advanced squamous cell NSCLC, and NSCLC not otherwise specified. Analysis of other EGFR variants within exons 22 to 24, or other applications related to NSCLC, is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes. At diagnosis, only analysis of somatic variants in exons 19 through 21 (eg, exon 19 deletions, L858R, T790M) within the EGFR gene, using the cobas EGFR Mutation Test v2, Guardant360 CDx test, OncoBEAM test, or InVisionFirst-Lung test with plasma specimens to detect circulating tumor DNA (ctDNA), **meets the definition of medical necessity** as an alternative to tissue biopsy to predict treatment response to an EGFR tyrosine kinase inhibitor therapy (eg, erlotinib [Tarceva], gefitinib [Iressa], afatinib [Gilotrif], dacomitinib [Vizimpro], or nswerctin [Tagrisso]) in members with advanced lung adenocarcinoma, large cell carcinoma, advanced squamous cell NSCLC, and NSCLC not otherwise specified. At progression, analysis of the EGFR T790M resistance variant for targeted therapy with nswerctin using ctDNA using the cobas EGFR Mutation Test v2, Guardant360 CDx test, OncoBEAM test, or InVisionFirst-Lung test with plasma specimens to detect ctDNA , **meets the definition of medical necessity** in members with advanced lung adenocarcinoma, large cell carcinoma, advanced squamous cell NSCLD, and NSCLC not otherwise specified when tissue biopsy to obtain new tissue is not feasible, e.g., in those who do not have enough tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue, do not have a biopsy-amenable lesion, or cannot undergo biopsy. **ALK Testing**

	Analysis of somatic rearrangement variants of the anaplastic lymphoma kinase (ALK) gene in tissue **meets the definition of medical necessity** to predict treatment response to ALK inhibitor therapy (e.g. crizotinib [Xalkori®], ceritinib [Zykadia™]), alectinib [Alecensa®], or brigatinib [Alunbrig™] in members with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (cases showing squamous cell histology). Analysis of somatic rearrangement variants of the ALK gene is considered **experimental or investigational** in all other applications related to NSCLC. The evidence is insufficient to determine the effects of the technology on health outcomes. Analysis of somatic rearrangement variants of the ALK gene using plasma specimens to detect ctDNA is considered **experimental or investigational** as an alternative to tissue biopsy to predict treatment response to ALK inhibitor therapy (eg, crizotinib [Xalkori], ceritinib [Zykadia], alectinib [Alecensa], or brigatinib [Alunbrig]) in members with NSCLC. **BRAF V600E Testing** Analysis of the somatic BRAF V600E variant in tissue **meets the definition of medical necessity** to predict treatment response to BRAF or MEK inhibitor therapy (eg, dabrafenib [Tafinlar] and trametinib [Mekinist]), in members with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (cases showing squamous cell histology). Analysis of somatic BRAF V600E variant is considered **experimental or investigational** in all other applications related to NSCLC. The evidence is insufficient to determine the effects of the technology on health outcomes. Analysis of the somatic BRAF V600E variant using plasma specimens to detect ctDNA is considered **experimental or investigational** as an alternative to tissue biopsy to predict treatment response to BRAF or MEK inhibitor therapy (eg, dabrafenib [Tafinlar], trametinib [Mekinist]) in members with NSCLC. The evidence is insufficient to determine the effects of the technology on health outcomes.

	KRAS Testing Analysis of somatic variants of the KRAS gene in tissue **meets the definition of medical necessity** to predict treatment response to sotorasib (Lumakras) in members with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded. Analysis of somatic variants of the KRAS gene using plasma specimens to detect ctDNA is considered **experimental or investigational** as a technique to predict treatment response to sotorasib(Lumakras). The evidence is insufficient to determine the effects of the technology on health outcomes. All other uses of analysis of somatic variants of the KRAS gene related to NSCLC are considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes. **ROS1 Testing** Analysis of somatic rearrangement variants of the ROS1 gene in tissue **meets the definition of medical necessity** to predict treatment response to ALK inhibitor therapy (crizotinib [Xalkori®]) in members with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (cases showing squamous cell histology). Analysis of somatic rearrangement variants of the ROS1 gene is considered **experimental or investigational** in all other applications related to NSCLC. The evidence is insufficient to determine the effects of the technology on health outcomes. Analysis of somatic rearrangement variants of the ROS1 gene using plasma specimens to detect ctDNA is considered **experimental or investigational** as an alternative to tissue biopsy to predict treatment response to ALK inhibitor therapy (crizotinib [Xalkori]) in members with NSCLC. The evidence is insufficient to determine the effects of the technology on health outcomes. **NTRK Gene Fusion Testing** Analysis of NTRK gene fusions **meets the definition of medical necessity** to predict treatment response to

	entrectinib (Rozlytrek) or nswerctinib (Vitrakvi) in members with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (cases showing squamous cell histology). Analysis of somatic NTRK gene fusions is considered **experimental or investigational** in all other applications related to NSCLC. The evidence is insufficient to determine the effects of the technology on health outcomes. **HER2 Testing** Analysis of genetic alterations in the HER2 gene for targeted therapy in members with NSCLC is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes. Analysis of somatic alterations in the HER2 gene using plasma specimens to detect ctDNA for targeted therapy in members with NSCLC is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes. **RET Rearrangement Testing** Analysis of somatic alteration in the RET gene in tissue **meets the definition of medical necessity** to predict treatment response to pralsetinib (Gavreto) or selpercatinib (Retevmo) in members with metastatic NSCLC. Analysis of somatic alterations in the RET gene is considered **experimental or investigational** in all other applications related to NSCLC. The evidence is insufficient to determine the effects of the technology on health outcomes. Analysis of somatic alterations of the RET gene using plasma specimens to detect ctDNA is considered **experimental or investigational** as an alternative to tissue biopsy to predict treatment response to RET inhibitor therapy (eg, selpercatinib [Retevmo], pralsetinib [Gavreto]) in members with NSCLC. The evidence is insufficient to determine the effects of the technology on health outcomes.

	MET Exon 14 Skipping Alteration Analysis of somatic alteration in tissue that leads to MET exon 14 skipping **meets the definition of medical necessity** to predict treatment response to capmatinib (Tabrecta) in members with metastatic NSCLC. Analysis of somatic alterations of the MET gene is considered **experimental or investigational** in all other applications related to NSCLC. The evidence is insufficient to determine the effects of the technology on health outcomes. Analysis of somatic alteration that leads to MET exon 14 skipping using plasma specimens to detect ctDNA is considered **experimental or investigational** as an alternative to tissue biopsy to predict treatment response to MET inhibitor therapy (capmatinib [Tabrecta]) in members with NSCLC. The evidence is insufficient to determine the effects of the technology on health outcomes. **PD-L1 Testing** PD-L1 testing **meets the definition of medical necessity** to predict treatment response to atezolizumab (Tecentriq), nivolumab (Opdivo) in combination with ipilimumab (Envoy), or pembrolizumab (Keytruda) in members with metastatic NSCLC. PD-L1 testing is considered **experimental or investigational** in all other applications related to NSCLC. The evidence is insufficient to determine the effects of the technology on health outcomes. **Tumor Mutational Burden Testing** Analysis of tumor mutational burden for targeted therapy in members with NSCLC is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes. **Plasma Testing When Tissue is Insufficient** Plasma tests for oncogenic driver variants deemed medically necessary on tissue biopsy **meets the definition of medical necessity** to predict treatment response to

	targeted therapy for members meeting the following criteria: • Member does not have sufficient tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue; **AND** • Follow-up tissue-based analysis is planned should no driver variant be identified via plasma testing. **Note**: A list of FDA-approved targeted treatments and companion diagnostic tests for NSCLC can be found at: fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools.
Molecular Markers in Fine Needle Aspirates of the Thyroid	The use of either the Afirma® Genomic Sequencing Classifier or ThyroSeq® in fine needle aspirates of the thyroid nodules with indeterminate cytologic findings (ie, Bethesda diagnostic category III [atypia/follicular lesion of undetermined significance] or Bethesda diagnostic category IV [follicular neoplasm/suspicion for a follicular neoplasm]) **meets the definition of medical necessity** in members who have the following characteristics: • Thyroid nodules without strong clinical or radiologic findings suggestive of malignancy AND • In whom surgical decision making would be affected by test results. The use of any of the following types of molecular marker testing or gene variant analysis in fine needle aspirates of thyroid nodules with indeterminate findings (Bethesda diagnostic category III [atypia/follicular lesion of undetermined significance] or Bethesda diagnostic category IV [follicular neoplasm/suspicion for a follicular neoplasm]) or suspicious findings [Bethesda diagnostic category V (suspicious for malignancy)] to rule in malignancy to guide surgical planning for initial resection rather than a 2-stage surgical biopsy followed by definitive surgery **meets the definition of medical necessity**: • ThyroSeq; • ThyraMIR® microRNA/ThyGenX® (ThyGeNEXT);

	• Afirma BRAF after Afirma Genomic Sequencing Classifier; or • Afirma MTC after Afirma Genomic Sequencing Classifier. Gene expression classifiers, genetic variant analysis, and molecular marker testing in fine needle aspirates of the thyroid not meeting criteria outlined above, including but not limited to use of RosettaGX Reveal and single-gene TERT testing, are considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes.
Holo-Transcobalamin	Measurement of holo-transcobalamin, including but not limited to its use in the diagnosis and management of vitamin B12 deficiency, is considered **experimental or investigational.** There is insufficient clinical evidence to support the use of the measurement of holo-transcobalamin to identify early states of vitamin B12 deficiency. There are inadequate data to establish holo-TC testing as an alternative to either serum cobalamin or levels of MMA or homocysteine.
Long-Chain Omega-3 Fatty Acids in Red Blood Cell Membranes	Measurement of long chain omega-3 fatty acids in red blood cell membranes is considered **experimental or investigational**, as there is insufficient clinical evidence to support the use of the measurement of long chain omega-3 fatty acids as a cardiac risk factor. There is a lack of scientific evidence in the published literature regarding how measurements of red blood cell omega-3 fatty acid would affect management of individuals at risk for or members with coronary artery disease (CAD).
Management of Pulmonary Nodules (REVEAL Lung Nodule Characterization)	Plasma-based proteomic screening, including but not limited to BDX-XL2 (Nodify XL2), in members with undiagnosed pulmonary nodules detected by computed tomography is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes. Gene expression profiling on bronchial brushings, including but not limited to Percepta® Bronchial Genomic Classifier, in members with indeterminate bronchoscopy results from undiagnosed pulmonary nodules is considered **experimental or investigational**. The evidence

	is insufficient to determine the effects of the technology on health outcomes.
Measurement of Serum Antibodies to Selected Biologic Agents (e.g. infliximab, adalimumab, vedolizumab, or ustekinumab) (LabCorp® Adalimumab Concentration & Anti-Adolimumab Antibody; Prometheus® nswer™ IFX; Prometheus® nswer™ ADA; Prometheus® nswer UST; Prometheus® nswer™ VDZ)	Measurement of antidrug antibodies in a member receiving treatment with a biologic agent, either alone or as a combination test, which includes the measurement of serum TNF blocking agent levels, is considered **experimental or investigational**. There is insufficient evidence in medical literature regarding the clinical utility and impact on clinical outcomes to permit conclusions on net health outcomes.
Gene Expression-Based Assays for Cancers of Unknown Primary (CancerTYPE ID®, MiRview® tests, Tissue of Origin®, ProOnc TumorSource DX™, RosettaGX Cancer Origin™ (formerly miRview® met^2).	Gene expression profiling is considered **experimental or investigational** to evaluate the site of origin of a tumor of unknown primary, or to distinguish a primary from a metastatic tumor. The evidence is insufficient to determine the effects of the technology on health outcomes.
Multianalyte Assays for Chronic Liver Disease	A single FibroSURE® multianalyte assay **meets the definition of medical necessity** for the evaluation of members with chronic liver disease. FibroSURE® multianalyte assays are considered **experimental or investigational** for monitoring members with chronic liver disease. The evidence is insufficient to determine the effects of the technology on health outcomes. The use of other multianalyte assays with algorithmic analyses (e.g. FIBROSpect® II) is considered **experimental or investigational** for the evaluation or monitoring of members with chronic liver disease. The evidence is insufficient to determine the effects of the technology on health outcomes.
Multibiomarker Disease Activity Score for Rheumatoid Arthritis	The use of a multibiomarker disease activity score for rheumatoid arthritis (eg, Vectra® DA score) is considered **experimental or investigational** in all situations. The

(Prism™ RA)	evidence is insufficient to determine the effects of the technology on health outcomes.
Multimarker Serum Testing Related to Ovarian Cancer	All uses of the OVA1®, Overa™, and ROMA™ tests are considered **experimental or investigational**, including but not limited to: • preoperative evaluation of adnexal masses to triage for malignancy • screening for ovarian cancer • selecting members for surgery for an adnexal mass • evaluation of members with clinical or radiologic evidence of malignancy • evaluation of members with nonspecific signs or symptoms suggesting possible malignancy, or • postoperative testing and monitoring to assess surgical outcome and/or to detect recurrent malignant disease following treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.
Pharmacogenomic and Metabolite Markers for Members Treated with Thiopurines	One-time genotypic or phenotypic analysis of thiopurine methyltransferase (TPMT) and nudix hydrolase (NUDT15) **meets the definition of medical necessity** in members beginning therapy with azathioprine (AZA), mercaptopurine (6-MP), thioguanine, or in members on thiopurine therapy with abnormal complete blood count (CBC) results that do not respond to dose reduction. Genotypic and/or phenotypic analysis of TPMT and NUDT15 is considered **experimental or investigational** for all other indications. The evidence is insufficient to determine the effects of technology on net health outcomes. Analysis of the metabolite markers of azathioprine (AZA) and mercaptopurine (6-MP), including 6-methyl-mercaptopurine ribonucleotides (6-MMRP) and 6-thioguanine nucleotides (6-TGN), is considered **experimental or investigational.** The evidence is insufficient to determine the effects of technology on net health outcomes.

Proteogenomic Testing for Members With Cancer	Proteogenomic testing of members with cancer (including but not limited to GPS Cancer™ test) is considered **experimental or investigational** for all indications. The evidence is insufficient to determine the effect of the technology on health outcomes.
Proteomic Testing for Advanced Non-Small Cell Lung Cancer (NSCLC)	Proteomic testing (VeriStrat®) **meets the definition of medical necessity** for members with advanced non-small cell lung cancer (NSCLC) meeting **ALL** of the following criteria: • tumor is wild-type (no mutation detected) EGFR **OR** with unknown EGFR status; • failed first-line systemic chemotherapy; **AND** • test results will determine whether to proceed with erlotinib (Tarceva®) therapy. Proteomic testing (VeriStrat) is considered **experimental or investigational** for all other indications. There is insufficient evidence to permit conclusions on clinical utility or net health outcomes.
Serum Biomarker Human Epididymis Protein 4 (Architect HE4 assay, Elecsys HE4, HE4 EIA Kit, HE4 immunoassay, Lumipulse G HE4 Immunoreaction)	Measurement of human epididymis protein 4 (HE4) is considered **experimental or investigational** for all indications. The evidence is insufficient to determine the effects of the technology on health outcomes.
Serum Biomarker Panel Testing for Systemic Lupus Erythematosus and Other Connective Tissue Diseases (Avise® CTD, Avise® Lupus, Avise® Monitor, Avise® MTX, Avise®, PG, Avise® Prognostic, Avise® SLE, Avise® SLE+)	Serum biomarker panel testing with proprietary algorithms and/or index scores for the diagnosis of systemic lupus erythematosus is considered **experimental or investigational.** The evidence is insufficient to determine the effects of the technology on health outcomes.
Serum Biomarker Tests for Multiple Sclerosis	Serum biomarker tests (e.g. gMS® Dx, gMS® Pro EDSS) for multiple sclerosis are considered **experimental or investigational** for all indications. There is insufficient evidence from prospective studies demonstrating improved health outcomes in individuals who may have multiple sclerosis and who are treated according to test results.

Uveal Melanoma	Gene expression profiling for uveal melanoma with DecisionDx-UM **meets the definition of medical necessity** for members with primary, localized uveal melanoma. Gene expression profiling for uveal melanoma that do not meet the above criteria is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes.

The following tumor markers are considered **experimental or investigational** for all indications, as there is insufficient evidence in the peer reviewed medical literature to support the use of these markers for screening, diagnosing, staging, surveillance or monitoring response to treatment:

Table 1

a2-PAG	pregnancy-associated alpha-2-glycoprotein
BCM	breast cancer mucin
CA50	cancer antigen 50
CA72-4	cancer antigen 72-4
CA195	cancer antigen 195
CA242	cancer antigen 242
CA549	carbohydrate antigen/cancer antigen 594
CA-SCC	squamous cell carcinoma antigen
CAM17-1	monocolonal antimucin antibody 17-1
CAM-26	monocolonal antimucin antibody 26
CAM-29	monocolonal antimucin antibody 29
CAR-3	antigenic determinant recognized by monoclonal antibody AR-3
DU-PAN-2	sialylated carbohydrate antigen DU-PAN-2
MCA	mucin-like carcinoma-associated antigen
NSE	neuron-specific enolase
P-LAP	placental alkaline phosphatase
PNA/ELLA	peanut lectin bonding assay
SLEX	sialylated Lewis X-I antigen
SLX	sialylated SSEA-1 antigen
SPAN-1	sialylated carbohydrate antigen SPAN-1
ST-439	sialylated carbohydrate antigen ST-439
TAG12	tumor-associated glycoprotein 12
TAG72	tumor-associated glycoprotein 72
TAG72.3	tumor-associated glycoprotein 72.3
TATI	tumor-associated trypsin inhibitor
TNF-a	tumor necrosis factor alpha
TPA	tissue polypeptic antigen

Home testing (including self-testing home kits) is considered **experimental or investigational** for all indications. The clinical validity of the tests have not been established and the evidence is insufficient to determine the effects of the technology on health outcomes.

The following tests are considered experimental or investigational, as there is insufficient evidence to support the use of these tests for all indications. Although there are ongoing clinical studies the current data are inadequate to permit scientific conclusions regarding the impact on management decisions and net health outcomes.

- Academic Profile
- Avise MCV
- Caris MI Cancer Seek™
- CellSearch® Circulating Multiple Myeloma Cell
- CellSearch® HER2 Circulating Tumor Cell
- Cxbladder™
- Darwin OncoTreat™ (formerly OncoTreat)
- Decipher® Bladder TURBT
- DetermaRx™ mRNA
- FiT IQ™
- GeneSearch™ BLN
- HeproDx-TM
- HERmark®
- InflammaDry®
- LC-MS/MS Targeted
- MSK-Impact™
- NETest
- Oncomap™ (formerly Oncotype MAP Pan-Cancer)
- Ova Check™
- OvaSure™
- PathwayFit®
- PGDx elio™ Tissue Complete
- PharmaRisk™
- Post-Op Px™ (previously known as ProstatePX)
- Praxis Extended RAS Panel
- PreDx Diabetes Risk Score™
- Prostate Px+
- ResponseDX: Lung™
- ResponseDX: Colon™
- Theralink
- Thyroid Cancer Mutation Panel.

BILLING/CODING INFORMATION:

Afirma® Genomic Sequencing Classifier

CPT Coding

81546	Oncology (thyroid), mRNA, gene expression analysis of 10,196 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious)

ICD-10 Diagnosis Codes That Support Medical Necessity (81545)

C73	Malignant neoplasm of thyroid gland
D44.0	Neoplasm of uncertain behavior of thyroid gland

Afirma® Xpression Atlas

CPT Coding

0204U	Oncology (thyroid), mRNA, gene expression analysis of 593 genes (including BRAF, RAS, RET, PAX8, and NTRK) for sequence variants and rearrangements, utilizing fine needle aspirate, reported as detected or not detected **(Investigational)**

BeScreened™-CRC

CPT Coding

0163U	Oncology (colorectal) screening, biochemical enzyme-linked immunosorbent assay (ELISA) of 3 plasma or serum proteins (teratocarcinoma derived growth factor-1 [TDGF-1, Cripto-1], carcinoembryonic antigen [CEA], extracellular matrix protein [ECM]), with demographic data (age, gender, CRC-screening compliance) using a proprietary algorithm and reported as likelihood of CRC or advanced adenomas **(Investigational)**

Biochemical Markers of Alzheimer's Disease

CPT Coding

0206U	Neurology (Alzheimer disease); cell aggregation using morphometric imaging and protein kinase C-epsilon (PKCe) concentration in response to amylospheroid treatment by ELISA, cultured skin fibroblasts, each reported as positive or negative for Alzheimer disease **(Investigational)**
0207U	Neurology (Alzheimer disease); cell aggregation using morphometric imaging and protein kinase C-epsilon (PKCe) concentration in response to amylospheroid treatment by ELISA, quantitative imaging of phosphorylated ERK1 and ERK2 in response to bradykinin treatment by in situ immunofluorescence, using cultured skin fibroblasts, reported as a probability index for Alzheimer disease (List separately in addition to code for primary procedure) **(Investigational)**

BRAF

CPT Coding

81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)

Breast Tumor Markers

CPT Coding

86300	Immunoassay for tumor antigen, Quantitative; CA 15-3 (27.29)

ICD-10 Diagnosis Codes That Support Medical Necessity (86300)

C50.011 – C50.929	Malignant neoplasm of breast
C79.2	Secondary malignant neoplasm of skin
C79.81	Secondary malignant neoplasm of breast
G89.3	Neoplasm related pain (acute) (chronic)
R97.8	Other abnormal tumor markers
Z85.3	Personal history of malignant neoplasm of breast

Cancer Antigen 125 (CA-125)

CPT Coding

86304	Immunoassay for tumor antigen, CA-125

ICD-10 Diagnosis Codes That Support Medical Necessity (86304)

C45.1	Mesothelioma of peritoneum
C48.1	Malignant neoplasm of specified parts of peritoneum
C48.2	Malignant neoplasm of peritoneum, unspecified
C48.8	Malignant neoplasm of overlapping sites of retroperitoneum and peritoneum
C53.0	Malignant neoplasm of endocervix
C53.1	Malignant neoplasm of exocervix
C54.1 – C54.9	Malignant neoplasm of corpus uteri
C56.1 – C56.9	Malignant neoplasm of ovary
C57.00 – C57.9	Malignant neoplasm of other and unspecified female genital organs
C79.60	Secondary malignant neoplasm of ovary, unspecified side
C79.61	Secondary malignant neoplasm of right ovary
C79.62	Secondary malignant neoplasm of left ovary
C79.82	Secondary malignant neoplasm of genital organs
C79.89	Secondary malignant neoplasm of other specified sites
D39.0 D39.10 – D39.12 D39.7 – D39.9	Neoplasm of uncertain behavior of female genital organs

G89.3	Neoplasm related pain (acute) (chronic)
R19.00	Intra-abdominal and pelvic swelling, mass and lump, unspecified site
R19.01	Right upper quadrant abdominal swelling, mass and lump
R19.02	Left upper quadrant abdominal swelling, mass and lump
R19.03	Right lower quadrant abdominal swelling, mass and lump
R19.04	Left lower quadrant abdominal swelling, mass and lump
R19.05	Periumbilical swelling, mass or lump
R19.06	Epigastric swelling, mass or lump
R19.07	Generalized intra-abdominal and pelvic swelling, mass and lump
R19.09	Other intra-abdominal and pelvic swelling, mass and lump
R97.1	Elevated cancer antigen 125 [CA 125]
R97.8	Other abnormal tumor markers
Z85.40	Personal history of malignant neoplasm of unspecified female genital organ
Z85.41	Personal history of malignant neoplasm of cervix uteri
Z85.42	Personal history of malignant neoplasm of other parts of uterus
Z85.43	Personal history of malignant neoplasm of ovary
Z85.44	Personal history of malignant neoplasm of other female genital organs

CancerType ID®

CPT Coding

81540	Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a probability of a predicted main cancer type and subtype **(Investigational)**

Cardiovascular Risk Panel: MI-HEART Ceramides

CPT Coding

0119U	Cardiology, ceramides by liquid chromatography-tandem mass spectrometry, plasma, quantitative report with risk score for major cardiovascular events **(Investigational)**

Caris MI Cancer Seek

CPT Coding

0211U	Oncology (pan-tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded tissue, interpretative report for single nucleotide variants, copy number alterations, tumor mutational burden, and microsatellite instability, with therapy association **(Investigational)**

CellSearch® Circulating Multiple Myeloma Cell

CPT Coding

0337U	Oncology (plasma cell disorders and myeloma), circulating plasma cell immunologic selection, identification, morphological characterization, and enumeration of plasma cells based on differential CD138, CD38, CD19, and CD45 protein biomarker expression, peripheral blood **(Investigational)**

CellSearch® HER2 Circulating Tumor Cell **CPT Coding**

0338U	Oncology (solid tumor), circulating tumor cell selection, identification, morphological characterization, detection and enumeration based on differential EpCAM, cytokeratins 8, 18, and 19, and CD45 protein biomarkers, and quantification of HER2 protein biomarker–expressing cells, peripheral blood **(Investigational)**

Cutaneous Melanoma

CPT Coding

0089U	Oncology (melanoma), gene expression profiling by RTqPCR, PRAME and LINC00518, superficial collection using adhesive patch(es) (**Investigational**)
0090U	Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 23 genes (14 content and 9 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical result (ie, benign, indeterminate, malignant) (**Investigational**)

Cxbladder™

CPT Coding

0012M	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and XCR2), utilizing urine, algorithm reported as a risk score for having urothelial carcinoma **(Investigational)**
0013M	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having recurrent urothelial carcinoma **(Investigational)**
0363U	Oncology (urothelial), mRNA, geneexpression profiling by real-time quantitative PCR of 5 genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm incorporates age, sex, smoking history, and macrohematuria frequency, reported as a risk score for having urothelial carcinoma (**Investigational**)

Darwin OncoTreat

CPT Coding

0019U	Oncology, RNA, gene expression by whole transcriptome sequencing, formalin-fixed paraffin embedded tissue or fresh frozen tissue, predictive algorithm reported as potential targets for therapeutic agents **(Investigational)**

Decipher Bladder TURBT

CPT Coding

0016M	Oncology (bladder), mRNA, microarray gene expression profiling of 219 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as molecular subtype (luminal, luminal infiltrated, basal, basal claudin-low, neuroendocrine-like) **(Investigational)**

DecisionDx DiffDx- Melanoma

CPT Coding

0314U	Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 35 genes (32 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical result (ie, benign, intermediate, malignant) (**Investigational**)

DecisionDx-Melanoma

CPT Coding

81529	Oncology (cutaneous melanoma), mRNA, gene expression profiling by real-time RT-PCR of 31 genes (28 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk, including likelihood of sentinel lymph node metastasis **(Investigational)**

DecisionDx-UM

CPT Coding

81552	Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis

ICD-10 Diagnosis Codes That Support Medical Necessity (81552)

C69.00-C69.92	Malignant neoplasm of eye and adnexa

DetermaRX mRNA

CPT Coding

0288U	Oncology (lung), mRNA, quantitative PCR analysis of 11 genes (BAG1, BRCA1, CDC6, CDK2AP1, ERBB3, FUT3, IL11, LCK, RND3, SH3BGR, WNT3A) and 3 reference genes (ESD, TBP, YAP1), formalin-fixed paraffin-embedded (FFPE) tumor tissue, algorithmic interpretation reported as a recurrence risk score **(Investigational)**

Epidermal Growth Factor Receptor (EGFR) Analysis

CPT Coding

81235	EGFR (epidermal growth factor receptor) (e.g., non-small cell lung cancer) gene analysis, common variants (e.g., exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)

Guardant360 CDx

CPT Coding

0242U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements

HeproDx-TM

CPT Coding

0006M	Oncology (hepatic), mRNA expression levels of 161 genes, utilizing fresh hepatocellular carcinoma tumor tissue, with alpha-fetoprotein level, algorithm reported as a risk classifier **(Investigational)**

InflammaDry®

InflammaDry® may be reported with CPT code 83516-Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step method.

KRAS Testing

CPT Coding

81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13) **(Investigational)**
81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146) **(Investigational)**

LC-MS/MS Targeted Proteomic

CPT Coding

0174U	Oncology (solid tumor), mass spectrometric 30 protein targets, formalin-fixed paraffin-embedded tissue, prognostic and predictive algorithm reported as likely, unlikely, or uncertain benefit of 39 chemotherapy and targeted therapeutic oncology agents **(Investigational)**

Measurement of Serum Antibodies to Selected Biologic Agents

CPT Coding

80145	Adalimumab (**Investigational**)
80230	Infliximab (**Investigational**)
80280	Vedolilzumab (**Investigational**)

MSK-Impact

CPT Coding

0048U	Oncology (solid organ neoplasia), DNA, targeted sequencing of protein-coding exons of 468 cancer-associated genes, including interrogation for somatic mutations and microsatellite instability, matched with normal specimens, utilizing formalin-fixed paraffin-embedded tumor tissue, report of clinically significant mutation(s) **(Investigational)**

Oncomap

CPT Coding

0244U	Oncology (solid organ), DNA, comprehensive genomic profiling, 257 genes, interrogation for single-nucleotide variants, insertions/deletions, copy number alterations, gene rearrangements, tumor-mutational burden and microsatellite instability, utilizing formalin-fixed paraffin-embedded tumor tissue **(Investigational)**

Circulating Tumor Cells/Liquid Biopsy

CPT Coding

86152	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood) **(Investigational)**
86153	Cell enumeration using immunologic selection and identification in fluid specimen (eg, circulating tumor cells in blood); physician interpretation and report, when required **(Investigational)**
0009U	Oncology (breast cancer), ERBB2 (HER2) copy number by FISH, tumor cells from formalin fixed paraffin embedded tissue isolated using image-based dielectrophoresis (DEP) sorting, reported as ERBB2 gene amplified or non-amplified **(Investigational)**

0091U	Oncology (colorectal) screening, cell enumeration of circulating tumor cells, utilizing whole blood, algorithm, for the presence of adenoma or cancer, reported as a positive or negative result (**Investigational**)
0179U	Oncology (non-small cell lung cancer), cell free DNA, targeted sequence analysis of 23 genes [single nucleotide variations, insertions and deletions, fusions without prior knowledge of partner/breakpoint, copy number variations], with report of significant mutation(s) (**Investigational**)

OVA1®

CPT Coding

81503	Oncology (ovarian), biochemical assays of five proteins (CA-125, apoliproprotein A1, beta-2 microglobulin, transferrin and pre-albumin), utilizing serum, algorithm reported as a risk score **(Investigational)**

Overa™

CPT Coding

0003U	Oncology (ovarian) biochemical assays of five proteins (apolipoprotein A-1, CA 125 II, follicle stimulating hormone, human epididymis protein 4, transferrin), utilizing serum, algorithm reported as a likelihood score **(Investigational)**

HE4 immunoassays & Kits

CPT Coding

86305	Human epididymis protein 4 (HE4) **(Investigational)**

Management of Pulmonary Nodules

CPT Coding

81554	Pulmonary disease (idiopathic pulmonary fibrosis [IPF]), mRNA, gene expression analysis of 190 genes, utilizing transbronchial biopsies, diagnostic algorithm reported as categorical result (eg, positive or negative for high probability of usual interstitial pneumonia [UIP]) **(Investigational)**
0080U	Oncology (lung), mass spectrometric analysis of galectin-3-binding protein and scavenger receptor cysteine-rich type 1 protein M130, with five clinical risk factors (age, smoking status, nodule diameter, nodule-spiculation status and nodule location), utilizing plasma, algorithm reported as a categorical probability of malignancy (**Investigational**)
0092U	Oncology (lung), three protein biomarkers, immunoassay using magnetic nanosensor technology, plasma, algorithm reported as risk score for likelihood of malignancy (**Investigational**)

Multianalyte Assays for Chronic Liver Disease

CPT Coding

81596	Infectious disease, chronic hepatitis C virus (HCV) infection, six biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, and haptoglobin) utilizing serum, prognostic algorithm reported as scores for fibrosis and necroinflammatory activity in liver
0002M	Liver disease, ten biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, haptoglobin, AST, glucose, total cholesterol and triglycerides) utilizing serum, prognostic algorithm reported as quantitative scores for fibrosis, steatosis and alcoholic steatohepatitis (ASH)
0003M	Liver disease, ten biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, haptoglobin, AST, glucose, total cholesterol and triglycerides) utilizing serum, prognostic algorithm reported as quantitative scores for fibrosis, steatosis and nonalcoholic steatohepatitis (NASH)
0166U	Liver disease, 10 biochemical assays (α2-macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, GGT, ALT, AST, triglycerides, cholesterol, fasting glucose) and biometric and demographic data, utilizing serum,algorithm reported as scores for fibrosis, necroinflammatory activity, and steatosis with a summary interpretation **(Investigational)**

NETest

CPT Coding

0007M	Oncology (gastrointestinal neuroendocrine tumors), real-time PCR expression analysis of 51 genes, utilizing whole peripheral blood, algorithm reported as a nomogram of tumor disease index **(Investigational)**

NTRK Gene Fusion Testing

CPT Coding

81191	NTRK1 (neurotrophic receptor tyrosine kinase 1) (eg, solid tumors) translocation analysis
81192	NTRK2 (neurotrophic receptor tyrosine kinase 2) (eg, solid tumors) translocation analysis
81193	NTRK3 (neurotrophic receptor tyrosine kinase 3) (eg, solid tumors) translocation analysis
81194	NTRK (neurotrophic-tropomyosin receptor tyrosine kinase 1, 2, and 3) (eg, solid tumors) translocation analysis

Pathwork Tissue of Origin®

CPT Coding

81504	Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores **(Investigational)**

PGDx elio Tissue Complete

CPT Coding

0250U	Oncology (solid organ neoplasm), targeted genomic sequence DNA analysis of 505 genes, interrogation for somatic alterations (SNVs [single nucleotide variant], small insertions and deletions, one amplification, and four translocations), microsatellite instability and tumor-mutation burden **(Investigational)**

Pharmacogenomic and Metabolite Markers for Members Treated With Thiopurines

CPT Coding

81335	TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3)
84433	Thiopurine S-methyltransferase (TPMT)
0034U	TPMT (thiopurine S-methyltransferase), NUDT15 (nudix hydroxylase 15)(eg, thiopurine metabolism) gene analysis, common variants (ie, TPMT *2, *3A, *3B, *3C, *4, *5, *6, *8, *12; NUDT15 *3, *4, *5)
0169U	NUDT15 (nudix hydrolase 15) and TPMT (thiopurine S-methyltransferase) (eg, drug metabolism) gene analysis, common variants

ICD-10 Diagnosis Codes That Support Medical Necessity (81335, 0034U, 0169U))

K50.00-K50.019	Crohn's disease of small intestine
K51.00-K51.319	Ulcerative colitis

Praxis Extended RAS Panel

CPT Coding

0111U	Oncology (colon cancer), targeted KRAS (codons 12, 13, and 61) and NRAS (codons 12, 13, and 61) gene analysis utilizing formalin-fixed paraffin-embedded tissue **(Investigational)**

PreDx Diabetes Risk Score™

CPT Coding

81506	Endocrinology (type 2 diabetes), biochemical assays of seven analytes (glucose, HbA1c, insulin, hs-CRP, adiponectin, ferritin, interleukin 2-receptor

	alpha), utilizing serum or plasma, algorithm reporting a risk score (Investigational)

ROMA™

CPT Coding

81500	Oncology (ovarian), biochemical assays of two proteins (CA-125 and HE4), utilizing serum, with menopausal status, algorithm reported as a risk score **(Investigational)**
86316**	Immunoassay for tumor antigen; other antigen, quantitative (e.g., CA 50, 72-4, 549), each **(Investigational)**

****May be covered when meets the definition of medical necessity when used to report the Chromogranin A (CgA) test for neuroendocrine tumors (i.e. carcinoid tumors).**

Serum Biomarker Panel Testing for Systemic Lupus Erythematosus and Other Connective Tissue Diseases

CPT Coding

0062U	Autoimmune (systemic lupus erythematosus), IgG and IgM analysis of 80 biomarkers, utilizing serum, algorithm reported with a risk score **(Investigational)**

Signatera™

CPT Coding

0340U	Oncology (pan-cancer), analysis of minimal residual disease (MRD) from plasma, with assays personalized to each patient based on prior next-generation sequencing of the patient's tumor and germline DNA, reported as absence or presence of MRD, with disease-burden correlation, if appropriate **(Investigational)**

TERT Testing

CPT Coding

81345	TERT (telomerase reverse transcriptase) (eg, thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (eg, promoter region) **(Investigational)**

Testing for ALK rearrangements and MET exon 14 skipping alterations using FoundationOne Liquid CDx

0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations (**Investigational**)

Theralink

CPT Coding

0249U	Oncology (breast), semiquantitative analysis of 32 phosphoproteins and protein analytes, includes laser capture microdissection, with algorithmic analysis and interpretative report **(Investigational)**

ThyGeNEXT®

CPT Coding

0245U	Oncology (thyroid), mutation analysis of 10 genes and 37 RNA fusions and expression of 4 mRNA markers using next generation sequencing, fine needle aspirate, report includes associated risk of malignancy expressed as a percentage

ThyraMIR™

CPT Coding

0018U	Oncology (thyroid), microRNA profiling by RT-PCR of 10 microRNA sequences, utilizing fine needle aspirate, algorithm reported as a positive or negative result for moderate to high risk of malignancy

ICD-10 Diagnosis Codes That Support Medical Necessity (0018U)

C73	Malignant neoplasm of thyroid gland
D44.0	Neoplasm of uncertain behavior of thyroid gland

Thyroseq®

CPT Coding

0026U	Oncology (thyroid), DNA and mRNA of 112 genes, next-generation sequencing, fine needle aspirate of thyroid nodule, algorithmic analysis reported as a categorical result ("Positive, high probability of malignancy" or "Negative, low probability of malignancy")

ICD-10 Diagnosis Codes That Support Medical Necessity (0026U)

C73	Malignant neoplasm of thyroid gland
D44.0	Neoplasm of uncertain behavior of thyroid gland

Thyroseq® CRC

CPT Coding

0287U	Oncology (thyroid), DNA and mRNA, next generation sequencing analysis of 112 genes, fine needle aspirate or formalinfixed paraffin-embedded (FFPE) tissue, algorithmic prediction of cancer recurrence, reported as a categorical risk result (low, intermediate, high) **(Investigational)**

Vectra®DA

CPT Coding

81490	Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score **(Investigational)**

VeriStrat®

CPT Coding

81538	Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival

ICD-10 Diagnosis Codes That Support Medical Necessity (81538)

C34.00 – C34.92	Malignant neoplasm of bronchus and lung

Tumor markers that do not have a specific CPT or HCPCS code may be reported with a nonspecific code such as CPT code 86316.

REIMBURSEMENT INFORMATION:

The following information is required documentation to support medical necessity: physician history and physical, physician progress notes, laboratory studies, treatment plan, and physician operative report (if applicable).

LOINC Codes

Documentation Table	LOINC Codes	LOINC Time Frame Modifier Code	LOINC Time Frame Modifier Codes Narrative
Physician history and physical	28626-0	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim
Attending physician progress note	18741-9	18805-2	Include all data of the selected type that represents observations made

			six months or fewer before starting date of service for the claim.
Plan of treatment	18776-5	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim.
Laboratory studies	26436-6	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim
Physician operative report	28573-4	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products:

The following National Coverage Determinations (NCD) located at www.cms.gov were reviewed on the last guideline reviewed date: Tumor Antigen by Immunoassay-CA 125 (190.28); Tumor Antigen by Immunoassay-CA 15-3/CA 27.29 (190.29); Tumor Antigen by Immunoassay-CA19-9 (190.30).

The following decision memo located at cms.gov was reviewed on the last guideline reviewed date: Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450N).

The following were reviewed on the last guideline reviewed date: MolDX LCDs located at palmettogba.com and cms.gov.

DEFINITIONS:

A2-PAG: pregnancy-associated alpha-2 glycoprotein (a chemical made by some cancers, consisting of a combination of protein and sugars).

BCM: breast cancer mucin; a marker made by some breast cancers.

CAM17-1, CAM26, CAM29: also known as monoclonal anti-mucin antibody markers, are markers noted in certain cancers.

CAR-3: a marker that reacts with a special test using a specific protein testing substance called “monoclonal antibody AR-3”.

Carbohydrate cancer antigens: CA 19-9, CA-125, CA 15-3/CA27-23, CA 242, CA 50, CA 72-4, CA 195, CA 549, M26, M29: these and other markers are a way to test for special markers on tumors, that are made of carbohydrates (a chemical that resembles a type of sugar).

CgA: a major protein of the granin family that has been described as a potential marker for neuroendrocrine tumors.

CellSearch®: a serum-based test that measures circulating tumor cells.

DU-PAN-2: a chemical (sialylated carbohydrate antigen) that may be found with some cancers.

FibroSpect II: serum marker panels for the diagnosis or clinical management of liver disease.

FibroSure: serum marker panels for the diagnosis or clinical management of liver disease.

GeneSearch BLN: an assay for the detection of greater than 0.2mm metastases in nodal tissue removed from sentinel lymph node biopsies of breast cancer patients.

HE4: an enzyme immunoassay for the quantitative determination of Human Epididymis Protein 4 (HE4) antigen in ovarian cancer.

LPA: lysophosphatidic acid; a chemical that has bee suggested as a possible test for ovarian cancer, body levels may be high in other cancers as well.

MCA: a chemical (Mucin-like Carcinoma-associated Antigen) that may be found in breast cancers.

MSA: a chemical (Mammary Serum Antigen) that may be found in breast cancers.

NSE: Neuron-Specific Enolase, a chemical made in the presence of some cancers.

Ova Check™: a serum-based test for the early detection of epithelial ovarian cancer.

OvaSure™: ovarian cancer-screening test that may be able to assess the presence of early stage ovarian cancer in high-risk woman.

Pathwork Tissue of Origin: a diagnostic test that may aid in the diagnosis of tumors with uncertain origins.

P-LAP: placental alkaline phosphatase, a chemical made in the presence of some cancers.

PNA/ELLA: peanut lectin bonding assay, a test for a certain tumor marker.

Proteogenomic Testing: involves the integration of proteomic, transcriptomic, and genomic information.

Proteomic Testing: the measurement of protein products *alone*, without integration of genomic and transcriptomic information.

SLEX, SLX: sialylated Lewis X-I antigen and sialylated SSEA-1 antigen.

SPAN-1: a sialylated carbohydrate antigen.

ST-439: a sialylated carbohydrate antigen.

TAG12, TAG 72, TAG 72.3: tumor associated glycoproteins; chemicals made by some cancers, consisting of a combination of protein and sugars.

TATI: tumor-associated trypsin inhibitor, a chemical made by the body, in the presence of some cancers.

TNF-a: tumor necrosis factor alpha, a chemical made by the immune system in the presence of some cancers.

TPA: tissue polypeptide antigen is a marker that may be present on some cancers.

RELATED GUIDELINES:

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer, 05-86000-26
Genetic Testing, 05-82000-28
KRAS, NRAS, and BRAF Variant Analysis (Including Liquid Biopsy & MicroRNA Expression Testing) in Metastatic Colorectal Cancer, 05-86000-28
Molecular Testing for the Management of Pancreatic Cysts, Barrett Esophagus, and Solid Pancreatic Lesions, 05-86000-27

OTHER:

None applicable.

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12. Blue Cross Blue Shield Association Evidence Positioning System®, 2.04.14, Evaluation of Biomarkers for Alzheimer Disease, 11/21.
13. Blue Cross Blue Shield Association Evidence Positioning System®, 2.04.19 Pharmacogenomic and Metabolite Markers for Patients Treated With Thiopurines, 12/21.
14. Blue Cross Blue Shield Association Evidence Positioning System®, 2.04.41 Noninvasive Techniques for the Evaluation and Monitoring of Patients with Chronic Liver Disease, 12/21.
15. Blue Cross Blue Shield Association Evidence Positioning System®, 2.04.45 Molecular Analysis (including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer, 12/21.
16. Blue Cross Blue Shield Association Evidence Positioning System®, 2.04.54 Gene Expression–Based Assays for Cancers of Unknown Primary, 04/22.
17. Blue Cross Blue Shield Association Evidence Positioning System®, 2.04.62, Multimarker Serum Testing Related to Ovarian Cancer, 01/22.
18. Blue Cross Blue Shield Association Evidence Positioning System®,2.04.66 Serum Biomarker Human Epididymis Protein 4, 01/22.
19. Blue Cross Blue Shield Association Evidence Positioning System®, 2.04.78 Molecular Markersin Fine Needle Aspirates of the Thyroid, 09/22.
20. Blue Cross Blue Shield Association Evidence Positioning System®, 2.04.84 Measurement of Serum Antibodies to Selected Biologic Agents, 12/21.
21. Blue Cross Blue Shield Association Evidence Positioning System®, 2.04.97 Microarray-Based Gene Expression Profile Testing for Multiple Myeloma Risk Stratification, 11/21.
22. Blue Cross Blue Shield Association Evidence Positioning System®, 2.04.100, Cardiovascular Risk Panels, 01/22.
23. Blue Cross Blue Shield Association Evidence Positioning System®, 2.04.119 Multibiomarker Disease Activity Blood Test for Rheumatoid Arthritis, 07/22.
24. Blue Cross Blue Shield Association Evidence Positioning System®, 2.04.120, Gene Expression Profiling for Uveal Melanoma, 03/22.
25. Blue Cross Blue Shield Association Evidence Positioning System®, 2.04.121, Miscellaneous Genetic and Molecular Diagnostic Tests, 08/22.
26. Blue Cross Blue Shield Association Evidence Positioning System®, 2.04.123, Serum Biomarker Panel Testing for Systemic Lupus Erythematosus and Other Connective Tissue Diseases, 07/22.

27. Blue Cross Blue Shield Association Evidence Positioning System®, 2.04.125 Proteomic Testing for Targeted Therapy in Non-Small-Cell Lung Cancer, 01/22.
28. Blue Cross Blue Shield Association Evidence Positioning System®, 2.04.140, Proteogenomic Testing for Patients With Cancer, 07/22.
29. Blue Cross Blue Shield Association Evidence Positioning System®, 2.04.141, Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy), 09/22.
30. Blue Cross Blue Shield Association Evidence Positioning System®2.04.142, Molecular Testing in the Management of Pulmonary Nodules, 06/22.
31. Blue Cross Blue Shield Association Evidence Positioning System®, 2.04.146 Gene Expression Profiling for Cutaneous Melanoma, 06/22.
32. Blue Cross Blue Shield Association Evidence Positioning System®, 2.04.150 Serologic Genetic and Molecular Screening for Colorectal Cancer, 08/22.
33. Blue Cross Blue Shield Association Evidence Positioning System®; 2.04.153 Tumor-Informed Circulating Tumor DNA Testing for Cancer Management, 05/22.
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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy & Coverage Committee on 10/27/22.

GUIDELINE UPDATE INFORMATION:

02/15/04	Developed separate guideline for non-covered tumor markers from the Tumor Markers guideline. Added program exception and added diagnoses [155.1, 156.1, 156.8, 156.9, 157.0 – 157.9, 197.8, 235.3, 235.5, V10.09] for 86301 for Medicare & More.
02/15/05	Deleted CA 19-9 from the investigational statement. Deleted Medicare program exception. Deleted the following from the when services are covered section of the MCG (per MPCC recommendation): Non-covered/investigational serum tumor markers may be covered if the individual subscriber has a benefit to cover non-covered/investigational services (refer to contract benefits). Updated related guidelines section.
08/15/07	Review, investigational status maintained, guideline reformatted, references updated.
09/15/08	Annual review: Position statements maintained. Description section and references updated.
08/15/09	Annual review: Guideline title changed, position statements updated, position statements from other tumor marker guidelines incorporated, description section, coding and references updated.
12/15/09	Updated the list of experimental/investigational tests.
01/01/10	Annual HCPCS coding update: added code 86305.
04/15/10	Updated the list of experimental/investigational tests and the Medicare Advantage program exception.
11/15/10	Revision; updated the list of experimental/investigational tests and added related ICD-10 codes.
08/15/11	Revision; Medicare Advantage and references updated; formatting changes.
01/01/12	Annual HCPCS update. Added CPT codes 0279T, 0280T.
04/01/12	Quarterly HCPCS update. Deleted HCPCS code S3711.
08/24/12	Reimbursement section updated.
10/15/12	Serum Antibodies for the Diagnosis of Inflammatory Bowel Disease position statement removed and added to the Genetic Testing guideline; reimbursement section updated.
11/15/12	List of experimental/investigational tests updated.
01/01/13	Annual HCPCS update. Added codes 81500, 81503, 81506, 86152, 86153, 0001M-0003M; deleted codes 0279T & 0280T.Updated position statement section and references.
02/15/13	Revision; position statement section and references updated.
03/15/13	Revision; position statement section including the list of investigational tests and references updated; title change.
05/15/13	Revision; position statement, billing/coding, program exception, and reference sections updated.
09/15/13	Revision; position statement section and references updated.
01/01/14	Annual HCPCS update. Added code 81504.
02/15/14	Revision; position statement section, Medicare program exception, and references updated.
06/15/14	Revision; position statement section, Coding, Medicare program exception, and references updated.

07/01/14	Quarterly HCPCS update. Added code 0007M.
10/15/14	Revision;Update the position statement and coding sections, program exception, and references.
01/01/15	Annual HCPCS/CPT update. Added codes 87505-87507.
06/15/15	Revision; position statement section, billing/coding, and references updated.
11/01/15	Revision: ICD-9 Codes deleted.
11/15/15	Revision; program exception and references updated.
01/01/16	Annual HCPCS/CPT update; codes 81490, 81538, 81540, 81545 added, code 0103T deleted.
03/15/16	Revision; position statement section, codeing and references updated.
09/15/16	Revision; position statement section, program exception, and references updated.
11/15/16	Revision; position statement section and references updated.
12/15/16	Revision; position statement, coding, and references updated.
02/01/17	Coding Update; new code 0003U added; investigational test list updated.
02/15/17	Revision; position statements, coding, and references updated.
03/15/17	Revision; Multianalyte assays for chronic liver disease position statements revised; coding and references updated.
04/15/17	Revision; Uveal Melanoma position statement added and references updated.
06/15/17	Revision; test names added to Biochemical Markers of Alzheimer's Disease & Circulating Tumor DNA position statements section; investigational test list updated.
07/15/17	Revision; Investigational test list updated.
08/01/17	Coding update; Added code 0009U.
12/15/17	Revision; Position statement section updated including the addition of ROS1 coverage statement; program exception and references updated.
01/01/18	Annual CPT/HCPCS update. Added code 0026U.
02/15/18	Revision; Circulating tumor DNA position statement added; OVA1, Overa, and ROMA tests position statement added and references updated.
04/01/18	Quarterly HCPCS/CPT update. Added codes 0012M and 0013M.
05/15/18	Revision; position statements, coding, and references updated.
09/15/18	Revision; position statements and references updated.
10/01/18	Quarterly HCPCS/CPT update. Added code 0062U.
12/15/18	Revision; Guardant360 test and OncoBEAM test added to the circulating tumor DNA for management of NSCLC position statement; investigational statement for microarray-based gene expression profile testing for multiple myeloma added; molecular analysis for targeted therapy of NSCLC position statements updated; coding, and references updated.
01/01/19	Annual CPT/HCPCS coding update. Added codes 81345, 81596; deleted code 0001M.
02/15/18	Revision; Fecal calprotectin testing position revised; coding and references updated.
05/15/19	Revision; Serum Biomarker Human Epididymis Protein 4 position statement added; references updated.
06/15/19	Revision; Xpresys test deleted (test no longer on the market).
07/01/19	Quarterly CPT/HCPCS update; Added codes 0089U-0092U. Revision; Gene expression profiling for cutaneous melanoma & molecular testing in the management of pulmonary

	nodules position statements added; OVA1 status maintained; coding and references updated.
08/15/19	Revision; Afirma test name updated.
01/01/20	Review; Analysis for targeted therapy of NSCLC & circulating tumor DNA for management of NSCLC statements updated; coding and references updated.Annual CPT/HCPCS coding update. Added codes 80145, 80230, 80280, 81552;deleted code 0081U.
04/01/20	Quarterly CPT/HCPCS update. Added code 0166U.
05/15/20	Coding and references updated.
07/01/20	Gene expression profiling for cutaneous melanoma reviewed and position statements maintained; references updated. Quarterly CPT/HCPCS update. Added codes 0174U & 0179U.
09/15/20	Revision; References updated.
09/18/20	Revision; Liquid biopsy test names updated.
10/01/20	Quarterly CPT/HCPCS update. Added codes 0016M, 0204U-0208U, and 0211U.
11/15/20	Revision; coding and references updated.
01/01/21	Annual CPT/HCPCS update. Codes 81191-81194,81529,81546,81554 added; codes 81545, 0111T deleted.
02/15/21	Review; Circulating tumor DNA management of NSCLC, molecular analysis for targeted therapy for NSCLC, measurement of serum antibodies to selected biologic agents, and pharmacogenomics markers for members treated with thiopurines position statements updated; coding and references updated.
04/01/21	Quarterly CPT/HCPCS update. Codes 0242U, 0244U, 0245U added.
04/16/21	Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy) statement added.
05/15/21	Revision; Homocysteine position statement deleted; investigational test list, coding and references updated.
06/15/21	Reimbursement section updated.
07/01/21	Quarterly CPT/HCPCS update. Codes 0249U and 0250U added.
08/15/21	Review; DecisionDx-Melanoma position statement maintained, references updated.
09/03/21	Revision: Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy) section updated.
10/15/21	Review; OVA1 position statement maintained, references updated.
11/15/21	Revision; Fecal Calprotectin position statement removed; coding and references updated.
01/01/22	Annual CPT/HCPCS coding update. Codes 0287U, 0288U added; 0090U revised; 0208U deleted.
02/15/22	Revision: Liquid biopsy for management of NSCLC position statements moved to the molecular analysis for targeted therapy or immunotherapy of NSCLC section; statements for KRAS testing for treatment with sotorasib added; coding and references updated.
04/01/22	Quarterly CPT/HCPCS update. Code 0314U added.
04/29/22	Codes 81445-81455 removed.
06/15/22	Expanded test panel list updated.

07/01/22	Review: Gene expression profiling for cutaneous melanoma position statements maintained; references updated. Quarterly CPT/HCPCS update: code 0016M revised.
08/15/22	Review: OVA1 position statement maintained; references updated.
09/15/22	Review: Comprehensive genomic profiling statement removed; investigational test list, coding section, and references updated.
10/01/22	Revision: Tumor-informed circulating tumor DNA testing for cancer management investigational statement added; references updated. Quarterly CPT/HCPCS update. Codes 0337U, 0338U, 0340U added; codes 0013U, 0014U, 0056U deleted.
11/15/22	Revision: Gene expression profiling for colorectal cancer statement added; coding and references updated.
01/01/23	Annual CPT/HCPCS coding update. Codes 84433 and 0363U added.